Title

Impact Of Weight Loss And Local Subcutaneous Fat On Knee Joint Synovitis Over 4 Years: Data From The Osteoarthritis Initiative

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initiated through dialogue between end-users and researchers with the goal of making injury prevention training an integral part of regular practice in youth handball through a series of studies. We have conducted studies within I-PROTECT and identified numerous barriers and facilitators, and address these determinants when designing the intervention.

Based on results from a first pilot version of exercises, the aim of the current study was to develop a full version of injury prevention education and training (i.e., the I-PROTECT intervention) specifically for youth handball players targeting end-users at the individual, team, and organizational levels through using knowledge from end-users and researchers/experts.

Methods: A full version of the I-PROTECT intervention (education and training) was developed in a co-creating process involving researchers/experts (sports medicine, sport psychology, handball, physical therapy, and/or strength and conditioning), and end-users (coaches, players, club administrators). End-users requested the intervention in a digital platform, therefore, a mobile application (I-PROTECT GO) was developed.

Results: End-user-targeted education and training was developed and made available in I-PROTECT GO, with modules for players, coaches, club administrators, and caregivers. All modules include general information about I-PROTECT and end-user-targeted current knowledge about injury prevention training (e.g., benefits of injury prevention training, physical and psychological principles, load-management). Additional content is available for coaches, players, and club administrators as follows: The coach module includes injury prevention physical and sport psychology exercises integrated within warm-up and handball skills training to be performed with their team; The player module includes injury prevention handball-specific strength exercises, sport psychology exercises, and 12 handball-specific injury prevention exercises from the coach module (to perform, e.g., during holiday breaks); The club administrator module includes education about implementation and an implementation checklist (e.g., goals, possible barriers and facilitators and solutions to address these, follow-up, maintenance, activities, roles and responsibilities). Consistent with requests conveyed by coaches and players, different programs are provided in the app over the season to support self-management and adoption. To increase motivation, the three basic psychological needs of Self-Determination Theory (i.e., autonomy, perceived competence, and relatedness) are utilized, in that players and coaches can change, add, progress the difficulty of exercises, and build their own program.

Conclusions: A process that engaged end-users and researchers/experts to develop injury prevention training specifically for youth handball, generated education and training targeting end-users at the individual, team, and organizational levels. The intervention content (education and training) was made available in an interactive mobile application (I-PROTECT GO), specifically developed within the I-PROTECT project, with modules for players, coaches, club administrators, and caregivers. Further studies will test and evaluate the intervention content and the mobile application.

O-17

IMPACT OF WEIGHT LOSS AND LOCAL SUBCUTANEOUS FAT ON KNEE JOINT SYNOVITIS OVER 4 YEARS: DATA FROM THE OSTEOARTHRITIS INITIATIVE

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Purpose: Synovitis and effusion are common in patients with OA and have been associated with pain and other clinical outcomes. Obesity is highly prevalent and a known risk factor for OA. However, being a modifiable risk factor, weight loss may slow cartilage degeneration, reduce pain, and functional disability. Previous work has shown that progression of synovitis is related to weight gain. The purpose of this study was to investigate the relationship of weight loss and of changes in subcutaneous fat around the knee on progression of knee joint synovitis over a period of 4 years.

Methods: We included 190 overweight and obese participants (body mass index [BMI] $\geq$25 kg/m^2) from the Osteoarthritis Initiative (OAI) who either lost weight (>10% weight loss, n=75) or had stable weight (<±3% weight change, n=115) over 4 years and were matched for age, sex, BMI at baseline. In the right knee, measurements of local subcutaneous fat (SCF) thickness (Fig. 1 and Fig. 3) and semi-quantitative effusion-synovitis scoring (Fig. 2 and Fig. 4) were performed in non-contrast enhanced MRI at baseline and 4-year follow-up using three-dimensional fast low-angle shot (3D-FLASH) and three-dimensional double-echo steady-state (3D-DESS) sequences, respectively. Local SCF measurements were performed in the medial, lateral, and anterior compartments of the knee. Effusion-synovitis assessments included the respective subscores of the MRI Osteoarthritis Knee Score (MOAKS), the Anterior Cruciate Ligament OsteoArthritis Score (ACLOAS), and a synovial proliferation score (SPS). Binary outcomes for worsening or improvement of synovitis scores (change in score <0 or >0, respectively) over 4 years were calculated. Logistic regression models were used for these outcomes with the primary predictor being decrease in SCF over 4 years (in mm) adjusted for age, sex, BMI, Kellgren-Lawrence (KL) grade, and diameter of the tibia at baseline. Statistical significance was defined by a p-value <0.05.

Results: The study group included 68 men and 122 women with an overall mean age of 64.4 ± 9.2 years and a mean BMI of 31.5 ± 3.9 kg/m^2 (Table 1). Worsening of effusion-synovitis scores was less frequently observed in participants with weight loss >10% compared to those with stable weight (ACLOAS 25.4% vs. 40.9%, MOAKS 30.9% vs. 39.2%, and SPS 25% vs. 26%, respectively). Absolute numbers of improvement of synovitis scores were low precluding further statistical analysis (Table 2). Worsening of MOAKS effusion-synovitis showed a significant negative association with decrease in lateral SCF (odds ratio=0.83 for 1 mm decrease in SCF, 95% confidence interval=0.72-0.96, p=0.01, Table 3, Fig. 3 and Fig. 4). Worsening of other effusion-synovitis scores did not show significant associations with changes in SCF.

	Weight loss >10% group	No weight change group (<±3% weight change)
Subjects, n	75	115
Women, n (%)	49 (65.3%)	73 (63.5%)
Age, years, mean (SD)	60.6 (9.4)	60.2 (9.1)
Baseline BMI, kg/m^2, mean (SD)	31.6 (4.0)	31.4 (3.9)
Weight loss over 48 mo, kg, mean (SD)	8.4 (12.1)	-0.3 (1.7)
KL-grade 0 at baseline, n (%)	21 (28.0%)	31 (27.0%)
KL-grade 1 at baseline, n (%)	20 (26.7%)	29 (25.2%)
KL-grade 2 at baseline, n (%)	24 (32.0%)	33 (28.7%)
KL-grade 3 at baseline, n (%)	10 (13.3%)	22 (19.1%)

Table 1: Characteristics of weight loss and no weight change groups

	Weight loss >10% group	No weight change group (<±3% weight change)
ACLOAS worsening, n (%)	17 (25.4%)	45 (40.9%)
MOAKS worsening, n (%)	21 (30.9%)	38 (39.2%)
SPS worsening, n (%)	17 (25.0%)	26 (26.0%)
ACLOAS improvement, n (%)	4 (6.0%)	9 (8.2%)
MOAKS improvement, n (%)	1 (1.5%)	8 (8.2%)
SPS improvement, n (%)	1 (1.5%)	3 (3.0%)

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Table 2: Frequencies of worsening and improvement of effusion-synovitis scores stratified by group

Outcome	Predictor	OR	95% CI for OR	P-value
ACLOAS worsening	Decrease in medial SCF	0.99	0.93, 1.05	0.71
…	Decrease in lateral SCF	0.89	0.78, 1.02	0.10
…	Decrease in anterior SCF	1.02	0.84, 1.25	0.82
MOAKS worsening	Decrease in medial SCF	0.99	0.93, 1.05	0.73
…	Decrease in lateral SCF	0.83	0.72, 0.96	0.01
…	Decrease in anterior SCF	0.93	0.76, 1.14	0.50
SPS worsening	Decrease in medial SCF	0.99	0.92, 1.05	0.69
…	Decrease in lateral SCF	0.95	0.83, 1.10	0.49
…	Decrease in anterior SCF	0.95	0.76, 1.17	0.60

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Table 3: Logistic regression to predict worsening of effusion-synovitis scores by mm decrease in SCF

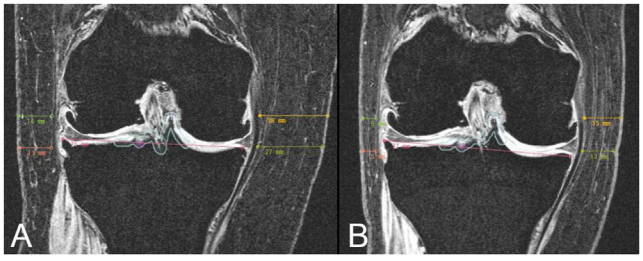

Fig. 1: Measurements of SCF in a 53-year-old women with weight loss over 4 years. Medial (yellow and olive) and lateral (green and red) measurements were performed at two levels (at the tip of the medial tibial spine and at the level of the medial joint space) and averaged. Anterior measurements were performed in sagittal reformations (not shown). This women with BMI=35.2 kg/m^2 at baseline (A) had lost 27.5 kg weight and showed decreased SCF around the knee after 4 years (B).

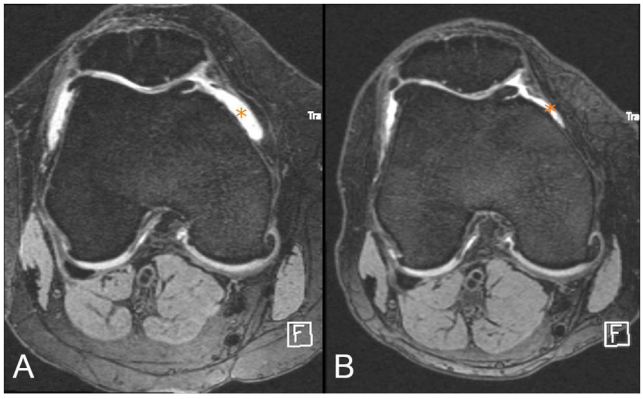

Fig. 2: Assessment of effusion-synovitis in a 53-year-old women with weight loss over 4 years (same as in Fig. 1). Images show medium amount of effusion at baseline (MOAKS=2, * in A) and a small amount of effusion and decreased SCF after 4 years (MOAKS=1, * in B).

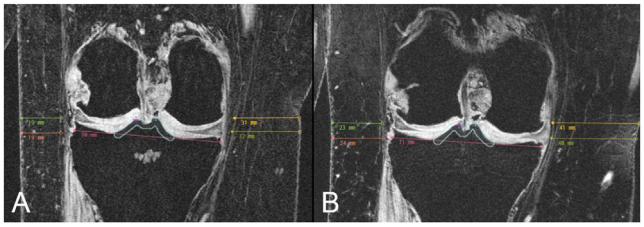

Fig. 3: Measurements of SCF in a 58-year-old women with stable weight over 4 years. Measurements were performed as described in Fig. 1. This women with BMI=39 kg/m^2 at baseline (A) had stable weight after 4 years and showed slightly increased SCF around the knee (B).

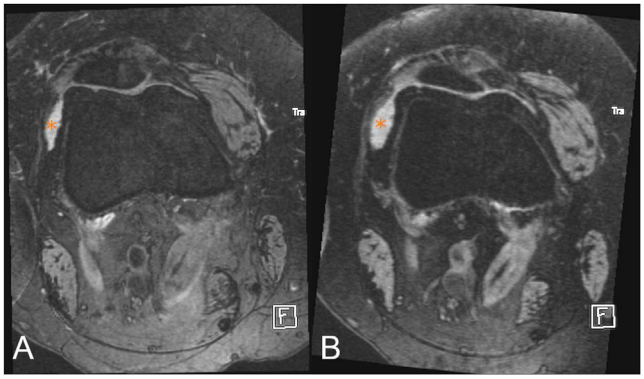

Fig. 4: Assessment of effusion-synovitis in a 58-year-old women with stable weight over 4 years (same as in Fig. 3). Images show small amount of effusion at baseline (MOAKS=1, * in A), that increases to medium amount of effusion after 4 years (MOAKS=2, * in B).

Conclusions: Investigating a group of obese participants from the OAI with weight loss and with stable weight over 4 years we found that for 1 mm decrease in SCF lateral to the knee joint the odds for aggravating effusion-synovitis decreased by 0.83. The significant, inverse relationship between SCF and synovitis was independent of BMI.

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NOD2 ATTENUATES OSTEOARTHRITIS VIA REPROGRAMMING INFLAMMATORY RESPONSE OF SYNOVIAL MACROPHAGES

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Purpose: Synovial inflammation, preceding other pathological changes in osteoarthritis (OA), is largely initiated by activation and M1 polarization of macrophages. Although highlighted in the orchestration of inflammatory process in OA, mechanism of activation and polarization of macrophages has not been comprehensively elucidated. Our previous study suggested nucleotide-binding oligomerization domain containing 2 (NOD2), one of the pathogen recognition receptors in innate immunity, as a potential regulator of macrophage activation, while its role in OA remains unclear, as well as its underlying mechanisms. This study aims to investigate the role of NOD2 in the pathogenesis of OA.

Methods: Expression of NOD2 in synovial tissue of human knee joint was investigated via immunohistochemical (IHC) staining and immunofluorescence (IF) staining. Impact of NOD2 on RAW264.7 macrophage activation and polarization upon stimulation of high-mobility group box-1 (HMGB1) was determined via knocking down and over-expression models *in vitro*, by quantitative polymerase chain reaction (qPCR), IF staining and flow cytometry. In order to investigate the paracrine effect of NOD2-overexpressed (oe-NOD2) macrophages on fibroblast-like synoviocytes (FLS) and chondrocytes, macrophages transfected with mock or oe-NOD2 lentiviruses were stimulated with HMGB1. And then, the supernatants were gathered, centrifuged to remove the cell debris, and applied to NIH3T3 fibroblasts and primary chondrocytes from male Sprague-Dawley rats aged 4 weeks. Proinflammatory phenotype of FLS and markers of chondrocyte metabolism were observed. Further, we explored the effect of *in vivo* over-expression of NOD2 via collagenase VII induced OA (CIOA) model in mice.

Results: NOD2 was significantly elevated in osteoarthritic synovial tissue, when compared with that of healthy synovial tissue (Fig. 1A, scale bar = 100μm). NOD2 showed consistent localization with F4/80 (surface marker of macrophages), indicating that macrophage was the principal residency of NOD2 in osteoarthritic synovial tissue (Fig. 1B, scale bar = 200μm). Targeted inhibition of NOD2 increased the expression of TNF-α in macrophages upon HMGB1 stimulation, while over-expression of NOD2 reduced the production of TNF-α (Fig. 1C, D), which was due to reprogramming of M1/M2 balance of macrophages (Fig. 1E). FLS developed polarized formation of lamellipodia (white arrows) upon HMGB1 stimulation, demonstrating characteristic colocalization with phosphorated focal adhesion kinase (p-FAK), suggesting proinflammatory phenotype with invading capability, while these features were reduced in the oe-NOD2 group (Fig. 2A). Besides, overexpression of macrophage NOD2 significantly enhanced the expression of anabolic factors in chondrocyte metabolism, including COL2A1, SOX9 and aggrecan, whereas the expression of catabolic factors in chondrocyte metabolism, such as MMP3, MMP13, ADAMTS4 and ADAMTS5, was downregulated (Fig. 2B). Further, we constructed CIOA mouse model, and showed that intra-articular injection of collagenase VII resulted in cartilage lesions, as was shown by Safranin O/fast green staining, while oe-NOD2 lentiviruses demonstrated significantly retention of articular cartilage, as was assessed via OARSI score (Fig. 3A, bar=100μm, Fig. 3C). Micro-CT scanning and 3D reconstruction revealed that quantity and volume of peri-articular osteophytes in the CIOA and CIOA + Mock group were both higher than the Ctrl group, while intra-articular injection of lentiviruses over-expressing NOD2 alleviated osteophyte formation in the CIOA + oe-NOD2 group (Fig. 3B, D, E).

Conclusions: This study provided novel insights into the involvement of innate immunity in OA pathogenesis, and highlighted NOD2 as a potential target for the prevention and treatment of OA.

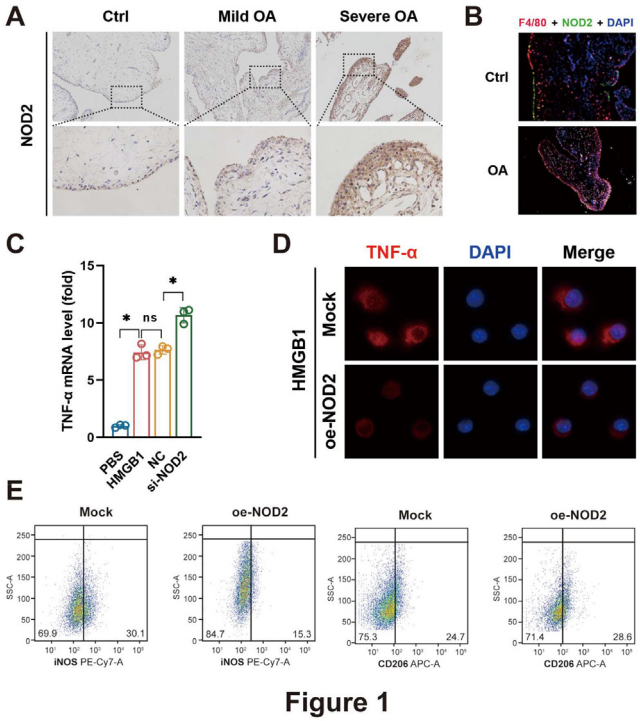

Figure 1